American Journal of Pathology, Vol. 156, No. 2, February 2000
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Short Communication

APC Mutations in Sporadic Medulloblastomas

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The cerebellar medulloblastoma (WHO Grade IV) is a highly malignant, invasive embryonal tumor with preferential manifestation in children. Several molecular alterations appear to be involved, including isochromosome 17q and the *p53*, *PTCH*, and β-catenin gene mutations. In this study, 46 sporadic medulloblastomas were screened for the presence of mutations in genes of the Wnt signaling pathway (*APC* and β-catenin). Single-strand conformational polymorphism (SSCP) analysis followed by direct DNA sequencing revealed 3 miscoding *APC* mutations in 2 (4.3%) medulloblastomas. One case contained a GCA→GTA mutation at codon 1296 (Ala→Val), and another case had double point mutations at codons 1472 (GTA→ATA, Val→Ile) and 1495 (AGT→GGT, Ser→Gly). Miscoding β-catenin mutations were detected in 4 tumors (8.7%). Three of these were located at codon 33 (TCT →TTT, Ser→Phe) and another at codon 37 (TCT→GCT, Ser→Ala). Adenomatous polyposis coli (*APC*) gene and β-catenin mutations were mutually exclusive and occurred in a total of 6 of 46 cases (13%). Although germline *APC* mutations are a well established cause of familial colon and brain tumors (Turcot syndrome), this study provides the first evidence that *APC* mutations are also operative in a subset of sporadic medulloblastomas. *(Am J Pathol 2000, 156:433–437)*

The adenomatous polyposis coli *(APC)* gene was originally identified as the target of germline mutations causing familial adenomatous polyposis (FAP), a syndrome of inherited predisposition to colon cancer.[1] The APC protein forms a complex with glycogen synthase kinase 3β (GSK-3β), thereby regulating the level of β-catenin protein, which functions as a downstream transcriptional activator of the Wnt signaling pathway[2,3] and is also the submembrane component of a cell-cell adhesion system.[2,4] GSK-3β phosphorylates β-catenin on specific serine/threonine residues on exon 3.[5] Somatic *APC* mutations are frequently found in sporadic colon cancer[6,7] and are considered the first genetic alteration[8] in the adenoma-to-carcinoma sequence. *APC* mutations typically lead to a truncated protein that lacks regulatory activity, causing β-catenin accumulation.[9] Up to 50% of colorectal carcinomas without *APC* mutation contain a β-catenin mutation, which also activates the Wnt pathway.[7]

The medulloblastoma (WHO Grade IV) is a malignant, invasive embryonal tumor of the cerebellum with a preferential manifestation in children.[10] Although the majority of medulloblastomas occur sporadically, some manifest within familial cancer syndromes including the naevoid basal cell carcinoma (Gorlin) syndrome[10] and Turcot syndrome, which is defined as manifestation of colorectal cancer and malignant brain tumor in the same patient. Turcot syndrome is heterogeneous, encompassing at least two subtypes.[11] One of these is characterized by the occurrence of glioblastoma in patients with hereditary non-polyposis colon cancer (HNPCC) and is caused by germline mutations in one of the DNA mismatch repair genes, such as *hPSM2* or *hMLH1*.[10] A second Turcot subtype is characterized by medulloblastoma in the setting of FAP and *APC* germline mutations. This raises the question of whether sporadic medulloblastomas also contain *APC* mutations. Previous attempts to identify *APC* mutations by an RNase protection assay failed.[12] Furthermore, loss of heterozygosity (LOH) on chromosome 5q, on which the *APC* gene is located, was not detected in 23 sporadic medulloblastomas.[13] However, a recent study showed that β-catenin mutations are present in 4% of cases,[14] suggesting the involvement of the Wnt signaling pathway in the development of sporadic medulloblastomas. In this study, we screened 46 sporadic medullo-

Supported by a grant from the Foundation for Promotion of Cancer Research, Japan. A. Sankila is a recipient of a grant from the Academy of Finland. M. B. Mahler-Araujo was supported by a grant from the Conselho National de Desenvolvimento Científico e Tecnológico, Brazil.

Accepted for publication October 19, 1999.

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blastomas for *APC* and β-catenin mutations using SSCP followed by direct DNA sequencing, and show that *APC* mutations occur in a small fraction of sporadic medulloblastomas that lack a β-catenin mutation.

Materials and Methods

Tumor Samples

Thirty-four medulloblastomas were obtained from the Department of Pathology, University Hospital Zurich (Zurich, Switzerland) and twelve from the Department of Pathology, School of Medicine of Ribeirao Preto, University of Sao Paulo (Sao Paulo, Brazil). The mean age of patients was 15.6 ± 13.5 years (range, 0.5–60 years). Twenty-seven patients were males and 19 were females. Tumors were fixed in buffered formalin and embedded in paraffin. DNA was extracted from paraffin sections as described previously.[15]

SSCP Analysis and Direct DNA Sequencing for β-Catenin Mutations

Pre-screening for mutations in exon 3 of human β-catenin gene, which contains the four potential GSK-3β phosphorylation sites,[16] was carried out by polymerase chain reaction (PCR)-SSCP analysis. Briefly, PCR was performed in a total volume of 10 μl, consisting of 2 μl of DNA solution, 0.5 U of *Taq* DNA polymerase (Sigma, St. Louis, MO), 0.5 μCi of [α-^{33}P]-dCTP (ICN Biomedicals, Inc., Costa Mesa, CA; specific activity, 3000 Ci/mmol), 1.5 mmol/L $MgCl_2$, 0.2 mmol/L of each dNTP, 0.4 μmol/L of both sense and antisense primers, 10 mmol/L Tris-HCl, pH 8.3, and 50 mmol/L KCl in the RoboCycler Gradient 96 (Stratagene, La Jolla, CA), with an initial denaturing step at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 1 minute, annealing at 53°C for 1 minute, and polymerization at 72°C for 1 minute, and a final extension of 5 minutes at 72°C. After amplification, 5 μl of PCR products were mixed with 12.5 μl loading buffer (95% formamide, 20 mmol/L EDTA, 0.05% xylene cyanol, and bromophenol blue), denatured at 95°C for 10 minutes, and quenched on ice. Four microliters of the above mixture were run on a 6% polyacrylamide nondenaturing gel containing 8% glycerol at 4 W for 14 hours at room temperature and/or on a 6% polyacrylamide nondenaturing gel containing 6% glycerol at 40 W for 3.5 hours with cooling by fan. Gels were dried at 80°C and autoradiographed for 12 to 48 hours. Primer sequences used were 5′-ATGGAACCAGACAGAAAAG-3′ (nt 254–272) and 5′-TACAGGACTTGGGAGGTATC-3′ (nt 386–405).

Samples that showed mobility shifts in the SSCP analysis were further analyzed by direct DNA sequencing. PCR was carried out as described above in the absence of [α-^{33}P]-dCTP. Five microliters of PCR products were digested with 1 U of shrimp alkaline phosphatase and 5 U of exonuclease I at 37°C for 15 minutes. After inactivation of these enzymes at 80°C for 15 minutes, primers (the same primers for PCR, 15 pmol) and 2 μl of 5× sequenase buffer (200 mmol/L Tris-HCl, pH 7.5, 100 mmol/L $MgCl_2$, 250 mmol/L NaCl) were added. Template-primer mixture was heated at 100°C for 5 minutes and then placed in ice-cold water. 0.1 mol/L dithiothreitol, 3 U Sequenase version 2.0 (USB, Cleveland, OH), and 0.5 μCi [α-^{33}P]-dATP or [α-^{33}P]-dCTP were added to samples, which were then divided into four wells, each containing termination mixture. Samples were incubated at 42°C for 6 minutes and mixed with 5 μl of stop solution (USB). After heating at 80°C for 3 minutes, samples were loaded onto a 6% polyacrylamide/7 mol/L urea gel and run at 70 W for 1.5 to 3 hours. Gels were dried at 80°C and autoradiographed for 12 to 48 hours. Samples were considered mutated only if the mutations were confirmed on two independent PCRs.

SSCP Analysis and Direct DNA Sequencing for APC Mutations

Codons 1255–1513 in exon 15 of the *APC* gene, which corresponds to the mutation cluster region and covers about two-thirds of all APC somatic mutations in colon tumors in FAP and non-FAP patients,[6,17] were screened for mutations by SSCP-direct DNA sequencing. The following primers were used for PCR amplification: 5′-AACCAAGAAACAATACAGA-3′ (sense) and (5′-CACTTTTGGAGGGAGATTT-3′ (antisense) to amplify codons 1255–1363 (fragment A), 5′-AGAATCAGCCAGGCACAAAG-3′ (sense) and 5′-GCTTGGTGGCATGGTTTGT-3′ (antisense) to amplify codons 1342–1433 (fragment B), and 5′-GCAGTGGAATGGTAAGTGG-3′ (sense) and 5′-TCATCGAGGCTCAGAGCA-3′ (antisense) to amplify codons 1410–1513 (fragment C). PCR was carried out in a total volume of 10 μl, consisting of 1 μl of DNA solution, 0.5 U of *Taq* DNA polymerase (Sigma), 0.5 μCi of [α-^{33}P]-dCTP (ICN Biomedicals; specific activity, 3000 Ci/mmol), 2.0 mmol/L (for fragment A) or 1.5 mmol/L (for fragments B and C) $MgCl_2$, 0.2 mmol/L of each dNTP, 0.4 μmol/L of both sense and antisense primers, 10 mmol/L Tris-HCl, pH 8.3, and 50 mmol/L KCl in the RoboCycler Gradient 96 (Stratagene), with an initial denaturation step at 95°C for 5 minutes, followed by 40 cycles of denaturation at 95°C for 60 sec, annealing at 47°C (for fragment A), 57°C (for fragment B) or 55°C (for fragment C) for 70 seconds, and polymerization at 72°C for 70 seconds, followed by a final extension of 5 minutes at 72°C. Five microliters of PCR products were mixed with 12.5 μl loading buffer (95% formamide, 20 mmol/L EDTA, 0.05% xylene cyanol, and bromophenol blue), denatured at 95°C for 10 minutes, and quenched on ice. Four microliters of this mixture were run on a 6% polyacrylamide nondenaturing gel containing 6% glycerol at 40 W for 5 hours with cooling by fan. Gels were dried at 80°C and autoradiographed for 12 to 48 hours.

Samples that showed mobility shifts in two independent SSCP analyses were further analyzed by direct DNA sequencing. For this, PCR amplifications were repeated as described above in the absence of [α-^{33}P]-dCTP. DNA sequencing was carried out using the same protocol as described above for sequencing of β-catenin mutations. The following internal primers were used: 5′-

Table 1. *APC* and β-Catenin Mutations in Sporadic Medulloblastomas

Case No.	Age (years)	Sex	*APC* mutation	β-Catenin mutation
325	1	F	codon 1443, CCT → CCA, Pro → Pro	–
331	2	F	codon 1472, GTA → ATA, Val → Ile codon 1495, AGT → GGT, Ser → Gly	–
321	5	F	–	codon 37, TCT → GCT, Ser → Ala
236	6	M	codon 1296, GCA → GTA, Ala → Val	–
340	9	F	–	codon 33, TCT → TTT, Ser → Phe
334	12	F	–	codon 33, TCT → TTT, Ser → Phe
248	34	M	–	codon 33, TCT → TTT, Ser → Phe

AATCAGACGACACAGGAAG-3′ (nt 3886–3904) and 5′-GGAACTTCGCTCACAGGAT-3′ (nt 3971–3989) for fragment A, and 5′-AAAACACCTCCACCACCTC-3′ (nt 4327–4345) and 5′-CTGGAAGAACCTGGACCCT-3′ (nt 4450–4468) for fragment C.

A polymorphism at codon 1493 (exon 15) of the *APC* gene (ACG/ACA, Thr/Thr) was detected in this study. To assess whether particular alleles are overrepresented in medulloblastomas, we also analyzed blood DNAs obtained from 50 healthy individuals in the United States for this polymorphism.

Statistical Analysis

Fisher's exact test was carried out to analyze the significance of allelic frequency difference in *APC* codon 1493 polymorphism between medulloblastoma patients and healthy individuals and to compare the frequencies of β-catenin and *APC* mutations in tumors developed in adults (older than 16 years) and in children.

Results

SSCP followed by direct DNA sequencing revealed 3 miscoding *APC* mutations in 2 medulloblastomas. One case (case 236) contained a GCA→GTA mutation at codon 1296 (Ala→Val) and another case (case 331) had double point mutations at codons 1472 (GTA→ATA, Val→Ile) and 1495 (AGT→GGT, Ser→Gly). Another biopsy (case 325) contained a silent mutation at codon 1443 (CCT→CCA, Pro→Pro). In all cases, the respective wild-type bases were also detectable. For case 236, adjacent nontumorous brain tissue was also analyzed and was shown to be wild-type, indicating that the *APC* mutation in this tumor was somatic (Table 1 and Figure 1). Patient 331 had no familial history of cancer at any site over three generations.

β-catenin mutations were found in 4 out of 46 (8.7%) medulloblastomas. Three were TCT→TTT mutations at codon 33, leading to an amino acid substitution from serine to phenylalanine. Another was a TCT→GCT (serine → alanine) mutation at codon 37 (Figure 1, Table 1). In all cases, the wild-type bases were also detectable. Adjacent nontumorous brain tissue was available in one case with a β-catenin mutation (case 248) and showed the β-catenin wild-type sequence. The occurrence of β-catenin and *APC* mutations was mutually exclusive.

A polymorphism at codon 1493 of the *APC* gene (ACG/ACA, Thr/Thr) was detected in this study. The frequency of A/A (14/44, 32%), G/G (6/44, 14%), and G/A (24/44, 54%) in medulloblastomas was similar to that in DNA from healthy Caucasian individuals: 20/50 (40%) for A/A, 3/50 (6%) for G/G, and 27/50 (54%) for G/A ($P = 0.2904$).

Discussion

The molecular basis of the development of medulloblastomas is still poorly understood. Isochromosome 17q, the most frequent genetic alteration, occurs in up to 50% of cases[18,19] and appears to be the cause of LOH at 17p, which is found in 30 to 45% of medulloblastomas.[20] The smallest deletions were observed at 17p13, which in-

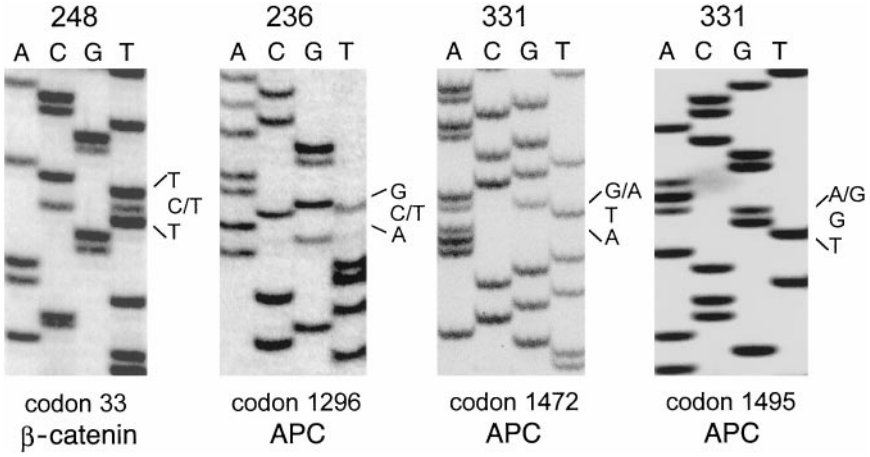

Figure 1. Representative DNA sequencing autoradiographs of β-catenin and APC mutations in sporadic medulloblastomas. Note that wild-type bases are detectable in all cases. The case numbers on the top correspond to those in Table 1.

cludes the *p53* locus, but the frequency of *p53* mutations in medulloblastomas is below 10%,[15,21] suggesting the presence of another tumor suppressor gene in this chromosomal region. The mapping to 17p13.3 of the hypermethylated in cancer (HIC-1) gene, which encodes a zinc-finger transcription factor, has raised the possibility that this gene may be involved in the development of medulloblastomas.[22] Translocation, deletions, and duplications of chromosome 1 were also frequently observed in medulloblastomas.[18,19] Rearrangements of chromosome 1 often result in trisomy 1q without loss of 1p. Mutations of the Patched gene *(PTCH)* are present in approximately 10% of medulloblastomas, with a preferential tendency for the desmoplastic variant.[23–25]

The present study provides the first evidence that *APC* mutations occur in sporadic medulloblastomas, albeit infrequently (4.3%). As observed in colon cancer,[7] β-catenin and *APC* mutations were mutually exclusive, suggesting that one of these alterations is sufficient to activate the Wnt signaling pathway. The failure in a previous study to detect *APC* mutations[12] may be due to the sensitivity of RNase protection assay used, which efficiently detects small deletions or insertions that lead to truncated protein but does not detect all point mutations.[6,17]

The *APC* mutations detected in sporadic medulloblastomas in this study were all missense mutations, whereas those in medulloblastoma patients with Turcot syndrome were trunctations.[12,26] Similarly, the majority of *APC* germline and somatic mutations in colon carcinomas are nonsense or frameshift mutations, leading to truncation of the APC protein.[6,7,27] However, 90% of mutations found in hepatoblastomas were missense mutations and only one was a frameshift mutation.[28] In gastric carcinomas, 30 to 50% of *APC* mutations found were missense mutations.[29–31] One *APC* mutation found in 39 pancreatic carcinomas[32] and both *APC* mutations found in 31 breast carcinomas[33] were missense mutations. It is of interest to note that all of the *APC* missense mutations detected in medulloblastomas in the present study (codons 1296, 1472, and 1495), as well as those in breast carcinomas (codons 1081 and 1096),[33] gastric carcinomas (codons 1120–1495),[29–31] hepatoblastomas (codons 1306–1534),[28] and pancreatic carcinomas (codon 1321),[32] were located in regions with three 15-amino acid consensus sequences (β-catenin binding sites) or seven 20-amino acid repeats (β-catenin and axin binding sites).[34,35] This suggests that *APC* missense mutations may affect the APC protein structure and impair its binding to β-catenin and/or axin.

In all cases with *APC* mutations, the respective wild-type bases were present (Figure 1). This is consistent with the previous studies showing that LOH involving the *APC* locus on chromosome 5q is a rare event in both familial (Turcot syndrome) and sporadic medulloblastmas.[12,13,26,36] Only 1 out of 7 medulloblastomas with a germline *APC* mutation in Turcot patients had lost the wild-type allele.[12,26] Similarly, none of 55 sporadic medulloblastomas showed LOH at the *APC* gene locus.[13,36] Truncated mutant APC proteins retaining the first 171 amino acids may oligomerize *in vivo* with wild-type proteins and inactivate them in a dominant negative manner.[37] It remains to be shown whether mutant APC proteins, due to missense mutations, act in a similar fashion to impair normal APC function.

In the present study, β-catenin mutations in exon 3 occurred in 4 of 46 (9%) sporadic medulloblastomas. Three of these were located at codon 33 and another was at codon 37. It is noteworthy that of the three mutations detected by Zurawel et al[14] in 67 sporadic medulloblastomas, two were also located at codon 33 and one at codon 37. This suggests that codons 33 and 37 are hot spots for β-catenin mutations in medulloblastomas. A similar clustering of mutations in codon 37 was observed in human bladder carcinomas.[38] In contrast, β-catenin mutations were randomly distributed at several serine/threonine residues in hepatocellular,[16] colorectal,[7] prostate,[39] and uterine carcinomas.[40]

The majority of medulloblastomas (70%) occur in children.[10] The histopathology of medulloblastoma in adults and in children is similar, but a tendency for longer survival of adult patients has been observed.[41] It is notable that in this study, 5 of 26 (19%) medulloblastomas in children (<16 years) carried a β-catenin or *APC* mutation but only 1 of 20 (5%) medulloblastomas in adults had a β-catenin mutation. This difference was not significant ($P = 0.2122$) and it remains to be shown in larger studies whether pediatric medulloblastomas carry genetic alterations different from those manifested in adults.

More than 20 polymorphisms have been identified in the *APC* gene. Among these, the I1307K polymorphism has been studied in detail and has been related to predisposition to colorectal cancer in Ashkenazi Jewish populations.[42] Little is known about the significance of other polymorphisms. In this study, we did not observe any I1307K polymorphism, but detected an *APC* polymorphism at codon 1493 (ACA/ACG), as previously reported.[17] DNA from medulloblastomas showed allelic patterns similar to those from healthy individuals, indicating that this polymorphism confers no risk for medulloblastoma.

In summary, the present study provides the first evidence that *APC* mutations are present in a subset of sporadic medulloblastomas. *APC* and β-catenin mutations were mutually exclusive and occurred in 6 of 46 (13%) cases, suggesting the involvement of the Wnt pathway in a subset of sporadic medulloblastomas. Codons 33 and 37 of the β-catenin gene constitute mutational hot spots in medulloblastomas.

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